A Prospective Follow-Up Study of Cancer Mortality in Relation to Serum DDT

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Abstract: Serum DDT and DDE levels were measured in 919 subjects in 1974 and 1975. Two-hundred and nine of the subjects died, including 54 from cancer, during a 10-year prospective follow-up period. There was no relation between either overall mortality or cancer mortality and increasing serum DDT levels. There was weak evidence of a positive relation between respiratory cancer mortality and serum DDT. The literature on DDT and human cancer is reviewed, and it is concluded that the evidence does not support the opinion that DDT is a human carcinogen. (*Am J Public Health* 1989; 79:43–46.)

Introduction

The widespread agricultural use of dichloro-diphenyl-trichloroethane (DDT) in the United States began in about 1945 and increased steadily until about 1960. At that time its use declined slightly because of increased resistance of pests to it. In June 1972, the United States Environmental Protection Agency (EPA) banned all crop uses of DDT. Outside the United States DDT is still used in agriculture, mainly for cotton crops, and for the control of insect-borne diseases, particularly malaria, in tropical countries.[1]

A major reason for the EPA ban of DDT was that it caused cancer in animals. DDT has been reported to induce liver tumors, lymphomas, and lung tumors in mice and liver tumors in some experiments with rats. On the other hand, feeding studies in hamsters were judged as negative, while those with dogs and monkeys are considered inconclusive.[2–4]

Because of recent litigation regarding putative exposure to DDT resulting from environmental contamination in Triana and other parts of northern Alabama, there is considerable public concern regarding the potential carcinogenicity of DDT in humans. There have been few epidemiologic studies of DDT and cancer, but some have reported an excess of lung cancer mortality among men occupationally exposed to DDT.[5,6] This analysis was undertaken, in part, because of this public concern and, in part, because of the suspected association between lung cancer and DDT.

DDT is metabolized very slowly by human beings, so that DDT metabolites are detectable in the fat and sera of people long after exposures end. This paper describes the overall mortality and the cancer mortality experience of a cohort of people whose serum DDT levels were measured in the mid-1970s and who were then followed prospectively for 10 years.

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Abbreviations used:
DDT = dichloro-diphenyl-trichloroethane
EPA = Environmental Protection Agency
PH = proportional hazards
RR = relative rate
SMR = standardized mortality ratio(s)
CI = confidence intervals

Methods

The study has been described in detail elsewhere.[7,8] In 1960, 2,283 adult residents of Charleston, South Carolina were enrolled in a prospective follow-up study. In 1974 and 1975 an attempt was made to obtain a venous blood sample from the 1,708 survivors of the original cohort (468 White men; 602 White women; 310 Black men, 328 Black women). Blood specimens were obtained for 304 White men, 327 White women, 204 Black men, and 84 Black women and analyzed for p,p′ DDT and p,p′ DDE by gas liquid chromatography using the Dale-Cueto modified method.[9,10] These 919 subjects comprise the cohort reported on here.

The subjects were recalled between 1984 and 1985 by which time 209 (23 per cent) had died. Seven-hundred of the subjects were determined to be alive, while the vital status of 10 was unknown (99 per cent follow-up rate). The cause of death among decedents was classified in two ways. First, the cause of death as listed on the death certificate was coded according to the 9th Revision of the International Classification of Diseases. Additionally, all deaths were reviewed by a medical committee and a cause of death was assigned by them on the basis of all available information. The determination of the medical committee is used to classify cause of death for internal comparisons comparing one group of study subjects with another. To compare study subjects with an external population, the encoded cause of death is used. Discrepancies between the two classifications account for slight differences in the number of cancer deaths in the internal and external analyses.

Statistical Procedures

Total serum DDT among study subjects was estimated by multiplying serum p,p′ DDE (in parts per billion) by 1.114 and adding to this serum, p,p′ DDT (ppb). This accommodated the slight reduction in the molecular weight of DDE after its metabolism from DDT. Since serum p,p′ DDT and p,p′ DDE comprise about 95 per cent of all serum DDT metabolites and isomers,[11] this combination of the two approximates total serum DDT. The distribution of serum DDT was examined among the 919 subjects and divided into terciles. The relative mortality rate (RR) was obtained for the second and third tercile using the lowest tercile as the referent category.

In the internal comparisons below, the relation between serum DDT and mortality is evaluated after adjustment for age, race, gender, years of schooling, and cigarette habit (non-smokers, ex-smokers, and current smokers) through the use of Cox's proportional hazards (PH) model.[12] Indicator variables were used to denote the terciles of DDT. The antilogarithm of the parameters from such a model is inter-

pretable as the RR of the cause of death of interest for persons in the second or third tercile compared with those in the first. Dose-response was evaluated by including the logarithm of serum DDT in a PH model or by assigning scores of 0, 1, and 2 for the first, second, and third terciles, respectively, and including this ordinal exposure variable in a PH model. The logarithm (base 10) of serum DDT was used as the continuous exposure since the distribution of serum DDT is asymmetric. The 10 subjects whose vital status is unknown were considered lost to follow-up at the midpoint of the interval between the date their blood was assayed and January 15, 1985.

As an additional test for association between serum DDT and mortality, the mean of the logarithm of serum DDT was compared for those who had died from all causes or from some specific cause with those who had not. These means were obtained from a multiple linear regression model which included terms for the potential confounders, an indicator variable denoting whether or not the individual had died of that cause, and with the logarithm of serum DDT as the outcome variable.

In addition to the internal analyses described above, the mortality experience of study subjects was compared to that of residents of the United States or of South Carolina. The age- (six 10-year groupings), gender-, and race-specific person-years of observation of subjects were obtained and the corresponding age-gender-race specific cancer mortality rates of the 1980 United States or South Carolina population were applied to those person-years to obtain an expected number of deaths.[13] The observed number of deaths divided by the expected number is the standardized mortality ratio (SMR). The Poisson distribution was used for the purposes of statistical testing and estimation.[14] All P-values in the results section are two-tailed.

Results

The median age of study subjects at the beginning of the follow-up period was 60 years (range: 39 to 89 years). The mean serum DDT level was 48 ppb with a standard deviation of 36 ppb (on the logarithm scale the mean is 1.59 and the standard deviation is 0.30). The mean level of serum DDT was about 6 per cent higher among men than women, and about 14 per cent higher among Blacks than Whites. Serum DDT levels increased with age and were lower among the more educated. The mean DDT levels were slightly lower among current and former cigarette smokers than among nonsmokers.

Internal Mortality Comparisons

The distribution of all deaths and of cancer deaths according to tercile of serum DDT is displayed in Table 1. The slight positive trend in overall mortality with increasing serum DDT is not significant either with the ordinal scale or the continuous logarithm measurement. The adjusted RRs are slightly lower than the unadjusted estimates, principally because of confounding by age and gender. The adjusted mean difference of the logarithm of serum DDT for decedents and the living is 0.025 (95 per cent confidence intervals = −0.02, 0.07).

There is no consistent positive trend in cancer mortality according to serum DDT. The adjusted mean of the logarithm of serum DDT is very slightly lower among persons who died of cancer than it is among those who did not (mean difference = −0.01, 95 per cent CI = −0.08, 0.07).

There is a slight positive trend in respiratory cancer rate according to tercile of serum DDT. However, the point estimates were unstable and the trend test p-values were high. Furthermore, the adjusted mean difference of the logarithm of serum DDT for those who had died of respiratory cancer compared with those who had not is 0.01 (95 per cent CI = −0.12, 0.14). As anticipated, cigarette smoking is a strong determinant of respiratory cancer mortality. The RRs of respiratory cancer for ex-smokers and current smokers compared with non-smokers are 8.3 (0.9, 77) and 24 (3.1, 193), respectively.

TABLE 1—Number of Deaths, Cancer Deaths, and Respiratory Cancer Deaths and the Relative Mortality Rates According to Terciles of Serum DDT

DDT Tercile	Number of Subjects	Person-Years	Deaths	Mortality Rate[a]	Relative Rate[b]
1 (0–31 ppb)	305	2,780	57	2,050	1.0
2 (31–52 ppb)	308	2,722	72	2,645	1.2 (0.8, 1.7)[c]
3 (>52 ppb)	306	2,646	80	3,023	1.2 (0.9, 1.8)
Trend test—ordinal					p = .27
Trend test—continuous					p = .21

DDT Tercile	Cancer Deaths	Mortality Rate[a]	Relative Rate[b]
1	15	540	1.0
2	23	845	1.5 (0.8, 3.0)
3	16	605	0.9 (0.4, 2.0)
Trend test—ordinal			p = .80
Trend test—continuous			p = .96

DDT Tercile	Respiratory Cancer Deaths	Mortality Rate[a]	Relative Rate[b]
1	5	180	1.0
2	7	257	1.5 (0.5, 4.9)
3	7	265	1.8 (0.5, 6.2)
Trend test—ordinal			p = 0.34
Trend test—continuous			p = 0.77

[a]Per 100,000 person-years.
[b]All relative rates are adjusted for age, gender, race, years of schooling, and cigarette habit.
[c]95% confidence intervals shown in parentheses.

TABLE 2—The Number of Observed Deaths, Cancer Deaths, and Respiratory Cancer Deaths and the Standardized Mortality Ratios

Referent Experience	All Deaths			Cancer Deaths			Respiratory Cancer Deaths		
	Observed	SMR	95% CI	Observed	SMR	95% CI	Observed	SMR	95% CI
United States	209	86	(75, 98)	58	98	(74, 126)	21	122	(76, 187)
South Carolina	209	81	(70, 93)	58	104	(79, 134)	21	124	(77, 189)

Seventeen persons died from cancer of the gastrointestinal system. There is a slight inverse relation between gastrointestinal cancer mortality and the logarithm of serum DDT. There were 18 other cancer deaths. No specific site included a number of deaths sufficient to permit a separate analysis. The RRs of all these other cancers for the second and third terciles compared with the first are 1.0 (0.3, 3.1) and 0.5 (0.1, 2.0), respectively.

External Mortality Analyses

The number of deaths and the SMRs for all causes, for cancer, and for respiratory cancer are displayed in Table 2. The overall mortality experience of study subjects was significantly lower than that of comparable individuals in the general population. The overall cancer mortality rate of study subjects was similar to that of the population of the United States and of South Carolina. On the other hand, the SMR for respiratory cancer mortality rate is higher, but not statistically significantly so, among study subjects.

Discussion

This study has a number of strengths for the purpose of evaluating the relation between DDT and cancer mortality, and at least one limitation, its small size. Strengths are that the follow-up was nearly complete and that the ascertainment and classification of cause of death was done without knowledge of the subjects' DDT levels. Furthermore, serum DDT was measured at the beginning of the follow-up period and so is not subject to distortion because of the presence of disease. Thus, the ascertainment of the outcome and the classification of the exposure are free of bias.

The exposure to DDT of this study population began in the late 1940s when it was used for mosquito control, in household pesticides, and for control of agricultural pests. Body burdens of DDT probably resulted from absorption through the skin and lungs and by ingestion. Subjects probably had been exposed chronically to DDT for at least 25 years by 1975, so that a reasonably long induction period would have elapsed.

Our subjects were not selected because of high DDT exposures, but their serum DDT levels were generally higher than among other comparable persons in the southern region. That is, if the age-gender-race structure of the study subjects is applied to the corresponding age-gender-race specific mean values of the logarithm of total serum DDT among southerners in the Second National Health and Nutrition Examination Survey,[11] an expected mean of 1.46 (about 35 ppb) is obtained, whereas the mean among our subjects is 1.59 (about 48 ppb). As another comparison, among 37 decedents aged 55 and over who had been occupationally exposed to pesticides,[17] the mean level of total serum DDT was about 92 ppb whereas among subjects in our upper tercile the mean is about 75 ppb. About 6 per cent of our study subjects had serum DDT levels exceeding 92 ppb. Thus, a number of our subjects apparently had sustained high DDT exposures.

A limitation of the study is that serum DDT and DDE serve as a surrogate measure of past DDT exposures. To the extent that current serum DDT levels are not an accurate indication of past DDT exposures, there will be random misclassification of the exposure and hence a bias in the direction of an absence of association between DDT and cancer. This is of special concern in a negative study such as this, but since DDT is metabolized very slowly, the bias probably is small.[15,16]

The findings of this study do not support the hypothesis that exposure to DDT increases cancer mortality. There is no consistent dose-response between cancer mortality rates and serum DDT levels and the mean level of serum DDT is lower among subjects who had died of cancer than it is among those who had not. Based upon the PH model of cancer mortality with the logarithm of serum DDT as the exposure measure, an upper 95 per cent confidence limit for the increase in cancer mortality sustained by a doubling of serum DDT is about 35 per cent. Thus, although the study includes only 54 cancer deaths, its findings effectively rule out a 50 per cent or more increase in overall cancer mortality attributable to a two-fold increase in serum DDT levels.

The findings with respect to respiratory cancer are less clear. Although there is some evidence of a dose-response relation between serum DDT and respiratory cancer, the point estimates are unstable and the trend is not statistically significant. Furthermore, respiratory cancer risk is lower among subjects in the upper quintile than it is among persons in the middle tercile. The finding that the mean levels of serum DDT are nearly identical for persons who had and had not died of respiratory cancer also does not support a causal interpretation of the finding. Based upon the respiratory cancer PH model it is estimated that a doubling of serum DDT is associated with only an 8 per cent increase in respiratory cancer mortality. On the other hand, the study is too small to exclude moderate increases in respiratory cancer mortality attributable to DDT. The upper 95 per cent confidence limit for excess respiratory cancer mortality associated with a doubling of serum DDT is 83 per cent.

The findings regarding other cancers also suffer from the imprecision resulting from a small study size. Nonetheless, the finding of an inverse relation between cancers of the gastrointestinal tract and cancers from all other sites combined, as well as the observation that no cluster of any particular form of cancer is evident among persons in the upper tercile of serum DDT, provides some assurance that DDT is not related to human cancer. The external SMR analysis indicates that the overall cancer mortality rate in the cohort is about the same as it is in the general population whereas the lung cancer mortality rate may be slightly higher.

Other epidemiologic studies generally do not support the opinion that DDT causes human cancer. In a retrospective follow-up study (RFUS) of pesticide applicators, the overall cancer SMR was 72 with 95 per cent confidence limits of 53 to 96.[18] In the same study the lung cancer SMR was 115 (77,

170), but the risk of lung cancer death was unrelated to duration of employment or the intensity of pesticide exposures. In another RFUS of pesticide applicators,[5] the lung cancer SMR was 135 (94, 189) and there was a consistent dose-response relation between length of licensure as a pesticide applicator and the lung cancer SMRs. In an East German study of agricultural applicators, a two-fold excess of lung cancer was reported.[6] Limitations of these studies are: 1) that these men had been exposed to other chemicals and pesticides so that it is impossible to attribute an excess of lung cancer among them specifically to DDT, and 2) the lack of information on their smoking habits also detracts from a causal interpretation of the findings.

Studies pertaining specifically to DDT do not support the opinion that it is related either to all cancer or to lung cancer mortality. In a follow-up study of workers occupationally exposed to pesticides, there was little difference between the serum DDT levels of persons who developed cancer or respiratory tract cancer as compared to those who did not.[17] In a study of 354 men employed at a plant that manufactured DDT,[19] the SMR for all cancer was 68 (25, 147), while the SMR for respiratory cancer was 125 (34, 321). In another study of workers engaged in the manufacture of DDT,[20] the SMR for all cancer was 99 (82, 119), while the SMR for lung cancer was 149 (68, 282), but in a nested case-control study among these and other workers, the RR of respiratory cancer among men exposed to DDT compared with those not so exposed was 0.74 (95% CI = 0.2 to 2.4, our estimate), while the RR of respiratory cancer pertaining to exposure to inorganic bromides was 7.0 (95% CI: 1.5 to 33, our estimate). This observation suggests that the excess of respiratory cancer observed among these DDT workers may have been due to some exposure other than DDT.

Higginson recently reviewed the epidemiologic evidence pertaining to DDT and cancer and concluded that DDT has had no significant impact on human cancer.[21] The present study supports this opinion. Nonetheless our findings with respect to respiratory cancer are not reassuring. On the one hand, there is a weak and not entirely consistent dose-response relation between serum DDT levels and respiratory cancer mortality that may be due to chance. On the other hand, previous epidemiologic studies have implicated pesticides (but not specifically DDT) as a cause of human lung cancer. Unfortunately, the issue of whether or not DDT is a weak lung carcinogen, or is associated with an increased risk of cancer of some rare site, can be resolved only in a study much larger than the present one.

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